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Mini Review

A mini-review of the associations between hypertension and risk of gallstone disease

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Abstract

A series of studies suggested that hypertension is significantly associated with the risk of gallstone disease (GSD). However, due to differences in study design, population stratification, sample size, and diagnostic criteria for GSD, the results of each study are inconsistent, limiting the strength and application of these pieces of evidence. We previously conducted a cross-sectional study incorporating over 300,000 population, and the results showed hypertension was significantly associated with the risk of GSD. However, it was a single-center study, and the external generalization of research results is limited to a certain extent. Thus, we conducted another multi-center study and a systematic review and meta-analysis to verify further the relationship between hypertension and the risk of GSD.

Keywords: Gallstone diseases, Hypertension, Multi-center study, Systematic review and meta-analysis

Introduction

Gallstone disease (GSD) is a common digestive system disease whose prevalence varies greatly depending on race and geographic location [1,2]. The plurality of GSD in western developed countries fluctuates from 10% to 20% and about 2% to 8% in Asian countries [3,4]. In addition, observational studies have reported that GSD is a significant risk factor for type 2 diabetes [5,6], gastrointestinal cancer [7], ischemic heart disease [8], and other diseases [9,10]. Its high prevalence and complication rate have caused severe medical and economic burdens on patients [11,12]. Identifying the risk factors for GSD to enhance and further intervention for high-risk groups is essential to reduce the burden of GSD further.

High blood pressure may play a critical role in forming gallstones [13]. Previous observational studies have shown that hypertension is significantly associated with GSD risk [4,14-20]. However, due to differences in study design, population stratification, sample size, and diagnostic criteria for GSD, the results of each study are inconsistent, limiting the strength and application of these pieces of evidence. We surveyed more than 300,000 subjects to explore the association between hypertension and GSD [21]. The results showed hypertension was correlated with GSD risk, and the association was not altered when stratified by sex and the severity of hypertension. Although with a relatively large sample size, it was just a single-center study, and the results need to be verified widely.

In this study, we intend to confirm further the relationship between hypertension and the risk of GSD by performing a multi-center cross-sectional study based on a survey of the health checkup population of four hospitals in China. Then, we conducted a systematic review and meta-analysis with trial sequential analysis (TSA) to verify these associations.

Methods

Published study

The published research analyzed the association between blood pressure and GSD risk by the logistic regression. During the analysis, the subjects were first divided into hypertension and non-hypertension to study the association between hypertension and gallstone disease. Then, according to the severity of hypertension, they were split into groups with normal blood pressure, high blood pressure, grade one, grade two, and grade three hypertension, respectively, to explore the association between hypertension and the risk of gallstone disease and the dose-response relationship. Finally, the association between GSD and systolic hypertension and diastolic hypertension per 5 mmHg increase was investigated.

Current study

The study recruited participants who underwent health checkups at four Chinese hospitals between January 2015 and May 2020. The four hospitals were as follows: the People's Hospital of Kaizhou District of Chongqing, the First Affiliated Hospital of Chongqing Medical University, Beijing Xiaotangshan Hospital, and Tianjin Medical University Cancer Institute and Hospital. Cholecystectomy was defined as a history of the gallbladder removal operation. GSD was diagnosed as the presence of gallstones and/or cholecystectomy [22].

The systematic review and meta-analysis followed the guidelines of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [23]. We systematically searched the Embase and Medline database to identify relevant English publications from inception to March 2021. Additionally, we retrieved China National Knowledge Infrastructure (CNKI) database, the Wanfang Data Knowledge Service Platform, and the Chinese Scientific Journal Database (VIP database) for eligible studies in Chinese. The keywords include "gallstone" OR "gallstone disease" OR "cholelithiasis" AND "hypertension" OR "blood pressure" OR "systolic blood pressure (SBP)" OR "diastolic blood pressure (DBP)" (PROSPERO; registration ID: CRD42021247589).

In the multi-center cross-sectional study, in each center, the relationship between hypertension (DBP/SBP) and GSD risk was assessed by multivariable logistic regression analysis. Subsequently, we pooled the regression results from each hospital using the meta-analysis method. In addition, we conducted subgroup analyses by subtype of GSD (gallstones or cholecystectomy), age (< 40, 40-60, > 60 years), and gender (male or female). Finally, we performed TSA to verify the reliability of the study results [24]. The evidence is considered sufficient and conclusive if the Z-curve passes through the TSA monitoring boundary or required information size (RIS) boundary. Otherwise, the association is inconclusive, and more studies are needed to verify the results further. All statistical analyses were performed using SPSS 26.0 (IBM, USA). Meta-analysis was performed by Stata 16 (Stata, College Station, TX). The statistically significant level was two-tailed and was set at p <0.05.

Results

A total of 633948 participants were enrolled in this study. Seventeen thousand thirty-eight subjects enrolled in the First Affiliated Hospital of Chongqing Medical University, 372,289 subjects in People's Hospital of Kaizhou District of Chongqing, 80,681 subjects in Beijing Xiaotangshan Hospital, and 10940 participants in Tianjin Medical University Cancer Institute and Hospital.

Multivariable regression analysis found that hypertension was significantly associated with the risk of GSD in each of the four hospitals (**Table 1**). As shown in **Figure 1**, pooled analyses showed that hypertension increased the risk of GSD. Subgroup analysis suggested hypertension was positively correlated with GSD risk in the young (age <40 years) and middle-aged (age: 40-60 years) population but not in the older (age >60 years). In addition, hypertension significantly increases the risk of GSD, and the higher grade of hypertension, the stronger association with GSD risk. Furthermore, we also found that each ten mmHg increase in SBP and DBP was positively associated with GSD risk. Subgroup analyses showed that each ten mmHg increase in SBP was associated with gallstones but not cholecystectomies.

As shown in **Figure 2**, our systematic review and meta-analysis showed hypertension was positively associated with the risk of GSD in previous studies. Similarly, after adding the results of our multi-center study, hypertension increased GSD risk by about 35%. The funnel plot showed no apparent asymmetry (**Supplementary Figure 1**). Moreover, Begg's (p = 0.100) and Egger's test (p = 0.423) indicated no significant difference in the publication bias **(Figure 2)**. Subgroup analyses by geographic location indicated that hypertension positively related to GSD in Asia and American countries but not in Europe (**Table 2**). Subgroup analysis by diagnosis showed hypertension was positively associated with gallstone subtypes but not with cholecystectomy (**Table 2**). Results showed the Z line both crossed the futility boundary and TSA monitoring boundary and achieved the RIS boundary, which suggested the association was conclusive (**Supplementary Figure 2**).

Furthermore, we investigated the differences in the DBP and SBP levels between GSD and the control group. The mean SBP and DBP level was higher in the GSD group than in the control group (**Figure 2**). And every one mmHg in SBP and DBP was significantly associated with increased GSD risk (**Figure 2**). Subgroup analyses indicated every one mmHg in SBP and DBP associated with GSD risk in a cross-sectional study and Asia population (**Table 2**).

Table 1. The association between blood pressure and GSD risk in each of the four centers.

	First affiliated Hospital of Chongqing Medical University		**The People's Hospital of Kaizhou District of Chongqing**		**Beijing Xiaotangshan Hospital**		**Tianjin Medical University Cancer Institute and Hospital**	
	OR (95%CI)	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
Gallstone Disease								
SBP_per 10 units	1.007 (0.988, 1.026)	0.478	1.015 (0.997, 1.034)	0.11	1.019 (0.991, 1.048)	0.185	1.063 (0.995, 1.135)	0.072
DBP_per 10 units	**1.042 (1.012, 1.072)**	**0.005**	1.011 (0.984, 1.039)	0.428	1.004 (0.960, 1.051)	0.861	1.018 (0.917, 1.131)	0.732
Hypertension	**1.153 (1.099, 1.210)**	**7.11×10^{-9}**	**1.065 (1.014, 1.118)**	**0.012**	**1.176 (1.089, 1.270)**	**3.28×10^{-5}**	**1.304 (1.055, 1.613)**	**0.014**
Grade 1	**1.058 (1.001, 1.117)**	**0.046**	**1.078 (1.020, 1.138)**	**0.007**	1.032 (0.945, 1.126)	0.482	**1.308 (1.038, 1.647)**	**0.023**
Grade 2	1.072 (0.975, 1.179)	0.153	1.048 (0.964, 1.139)	0.273	0.926 (0.785, 1.093)	0.365	1.352 (0.997, 1.834)	0.052
Grade 3	**1.177 (1.054, 1.315)**	**0.004**	0.996 (0.865, 1.147)	0.956	0.866 (0.569, 1.318)	0.502	1.105 (0.659, 1.854)	0.705
Subgroup analysis by age								
<40 years								
SBP_per 10 units	0.962 (0.914, 1.013)	0.138	**0.915 (0.861, 0.973)**	**0.005**	0.995 (0.901, 1.098)	0.918	1.001 (0.776, 1.290)	0.994
DBP_per 10 units	**1.136 (1.060, 1.217)**	**3.15×10^{-4}**	**1.106 (1.025, 1.195)**	**0.01**	1.082 (0.940, 1.246)	0.273	1.176 (0.842, 1.643)	0.34
Hypertension	**1.214 (1.053, 1.399)**	**0.007**	1.059 (0.896, 1.252)	0.502	1.156 (0.524, 2.548)	0.72	1.582 (0.824, 3.038)	0.168
40 - 60 years								
SBP_per 10 units	1.013 (0.983, 1.043)	0.397	1.010 (0.985, 1.035)	0.452	1.019 (0.975, 1.065)	0.406	1.047 (0.940, 1.167)	0.402
DBP_per 10 units	1.039 (0.994, 1.085)	0.088	**1.039 (1.002, 1.078)**	**0.04**	1.058 (0.987, 1.134)	0.11	1.027 (0.869, 1.214)	0.756
Hypertension	**1.155 (1.083, 1.233)**	**1.37×10^{-5}**	**1.068 (1.005, 1.135)**	**0.034**	1.060 (0.872, 1.287)	0.56	1.104 (0.825, 1.476)	0.507
>60 years								
SBP_per 10 units	**1.045 (1.016, 1.075)**	**0.002**	**1.058 (1.026, 1.091)**	**3.23×10^{-4}**	1.013 (0.974, 1.054)	0.518	1.075 (0.981, 1.177)	0.121
DBP_per 10 units	0.962 (0.917, 1.010)	0.122	**0.904 (0.859, 0.950)**	**8.55×10^{-5}**	**0.906 (0.845, 0.971)**	**0.005**	0.970 (0.829, 1.135)	0.705
Hypertension	**1.148 (1.056, 1.248)**	**0.001**	1.056 (0.961, 1.160)	0.259	0.902 (0.736, 1.107)	0.324	**1.483 (1.027, 2.140)**	**0.035**
Subgroup analysis by gender								
Male								
SBP_per 10 units	0.979 (0.952, 1.007)	0.134	0.993 (0.966, 1.020)	0.603	1.017 (0.981, 1.054)	0.363	**1.103 (1.002, 1.214)**	**0.044**

DBP_per 10 units	**1.076 (1.033, 1.120)**	**4.39×10^{-4}**	1.016 (0.978, 1.056)	0.416	1.006 (0.949, 1.066)	0.835	1.012 (0.869, 1.177)	0.881
Hypertension	**1.133 (1.065, 1.205)**	**7.38×10^{-5}**	1.011 (0.948, 1.078)	0.742	**1.206 (1.097, 1.325)**	**1.05×10^{-4}**	**1.495 (1.112, 2.010)**	**0.008**
Female								
SBP_per 10 units	**1.047 (1.020, 1.075)**	**0.001**	**1.038 (1.012, 1.065)**	**0.004**	1.018 (0.973, 1.065)	0.438	1.026 (0.935, 1.125)	0.594
DBP_per 10 units	0.996 (0.956, 1.039)	0.868	1.007 (0.969, 1.047)	0.714	1.008 (0.937, 1.084)	0.838	1.020 (0.881, 1.182)	0.787
Hypertension	**1.187 (1.098, 1.283)**	**1.70×10^{-5}**	**1.146 (1.062, 1.237)**	**4.36×10^{-4}**	1.117 (0.980, 1.274)	0.098	1.111 (0.814, 1.515)	0.508
Subgroup analysis by diagnosis								
Gallstones								
SBP_per 10 units	**1.030 (1.004, 1.057)**	**0.025**	**1.048 (1.021, 1.076)**	**4.32×10^{-4}**	1.029 (0.996, 1.063)	0.085	**1.091 (1.009, 1.179)**	**0.028**
DBP_per 10 units	1.024 (0.985, 1.065)	0.233	0.982 (0.945, 1.021)	0.367	1.011 (0.959, 1.066)	0.679	0.995 (0.880, 1.125)	0.934
Hypertension	**1.141 (1.067, 1.221)**	**1.13×10^{-4}**	**1.096 (1.022, 1.175)**	**0.011**	**1.251 (1.144, 1.367)**	**7.75×10^{-7}**	**1.370 (1.067, 1.758)**	**0.013**
Grade 1	1.067 (0.988, 1.152)	0.098	**1.087 (1.005, 1.176)**	**0.038**	1.101 (0.996, 1.217)	0.059	1.276 (0.969, 1.681)	0.083
Grade 2	**1.153 (1.013, 1.314)**	**0.031**	1.054 (0.935, 1.189)	0.387	1.007 (0.835, 1.216)	0.938	**1.623 (1.147, 2.298)**	**0.006**
Grade 3	**1.473 (1.277, 1.698)**	**9.75×10^{-8}**	1.307 (1.090, 1.568)	0.004	0.892 (0.549, 1.448)	0.643	1.397 (0.783, 2.491)	0.257
Cholecystectomy								
SBP_per 10 units	0.981 (0.957, 1.006)	0.144	0.984 (0.961, 1.008)	0.182	0.990 (0.942, 1.041)	0.708	0.996 (0.887, 1.119)	0.947
DBP_per 10 units	**1.058 (1.017, 1.100)**	**0.005**	**1.038 (1.002, 1.076)**	**0.038**	0.989 (0.911, 1.074)	0.793	1.064 (0.883, 1.283)	0.512
Hypertension	**1.138 (1.067, 1.214)**	**8.46×10^{-5}**	1.032 (0.968, 1.100)	0.336	0.986 (0.858, 1.134)	0.846	1.122 (0.770, 1.637)	0.548
Grade 1	1.040 (0.967, 1.118)	0.295	1.060 (0.987, 1.138)	0.108	0.871 (0.739, 1.026)	0.097	1.310 (0.881, 1.947)	0.182
Grade 2	0.990 (0.873, 1.124)	0.882	1.037 (0.931, 1.154)	0.511	0.757 (0.550, 1.042)	0.088	0.831 (0.466, 1.482)	0.531
Grade 3	0.903 (0.774, 1.053)	0.193	**0.761 (0.621, 0.932)**	**0.008**	0.821 (0.383, 1.757)	0.611	0.611 (0.214, 1.747)	0.358

DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure

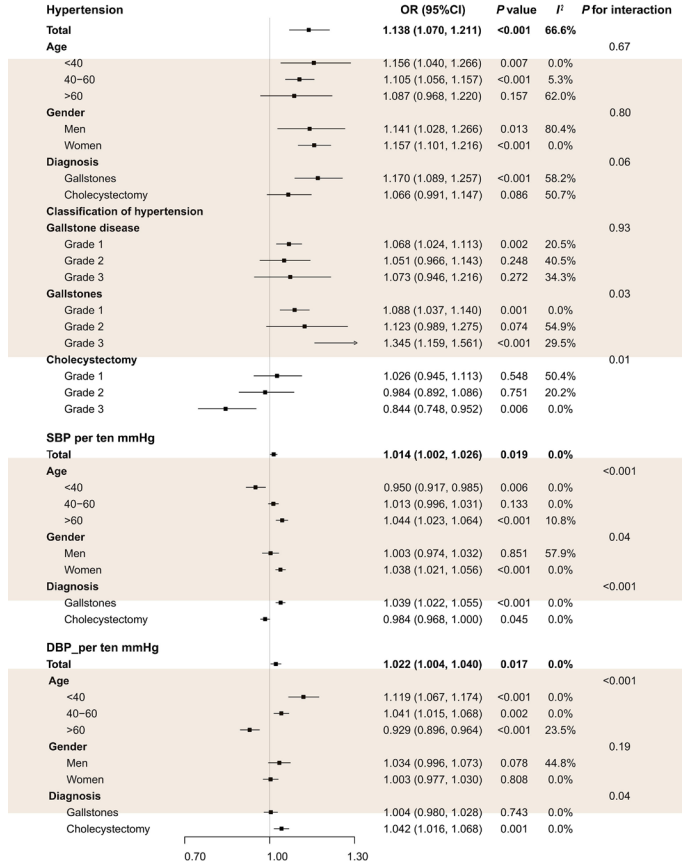

Figure 1: Pooled analysis of the association between blood pressure and gallstone diseases risk in the multi-center study.

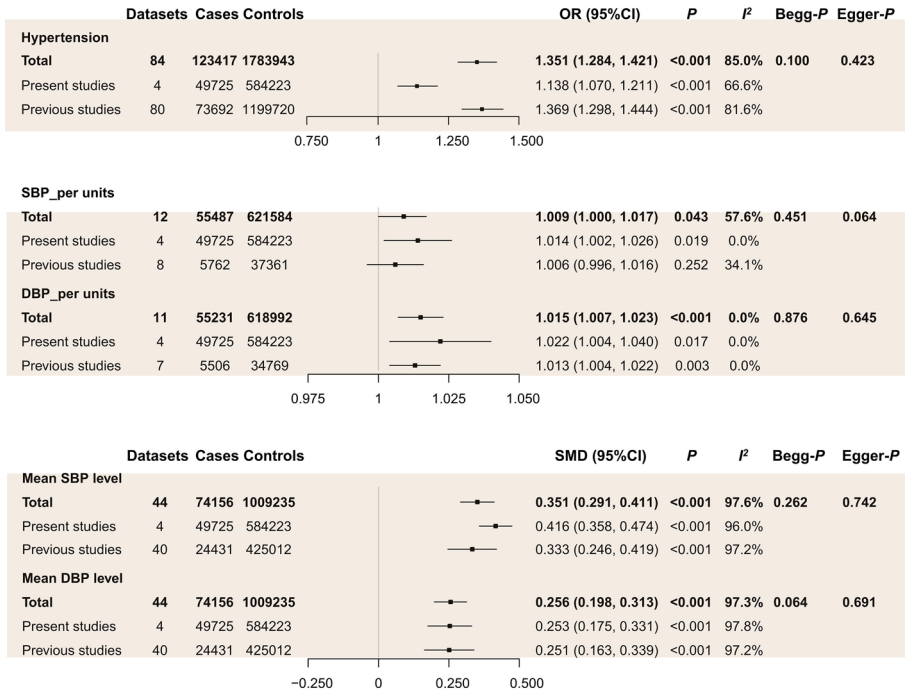

Figure 2: Meta-analysis of the association between blood pressure and GSD risk.

Discussion

This study explores the relationship between hypertension and the risk of GSD based on our published research and some current study findings. In both studies, hypertension was found to be positively correlated with the risk of GSD, and the higher grade of hypertension, the stronger association with gallstone formation.

Consistent with the results of this study, a cross-sectional survey in the Shanghai population [4] also found that hypertension significantly increased the risk of GSD after multi-factor adjustment. A cohort study in the Korean population suggested that hypertension was an independent risk factor for GSD in both genders [16]. However, some studies have shown the opposite conclusion. A case-control study conducted by Gonzalez-Perez and colleagues in the UK population concluded that hypertension is not significantly associated with GSD [20]. A cohort study conducted in the USA population suggested that 0hypertension was not a risk factor for GSD in both genders [25]. These data indicated that the paradoxical results might be due to differences in experimental design, study population, sample size, diagnostic criteria for GSD, or interference from other factors.

The mechanisms of hypertension in GSD remain unclear so far. Evidence has shown that there are common risk factors or pathogenic factors between cholelithiasis and hypertension, such as lipid metabolism [26,27] and insulin resistance [28-31] lipid metabolism has long been a research focus in GSD etiology, which is also associated with hypertension [26]. High levels of HDL-C facilitate hepatic bile acid synthesis [32] and decrease the cholesterol saturation index [33,34], which increases cholesterol solubility [35] and thus protects against the formation of gallstones. In addition, insulin resistance is associated with both hypertension and GSD. Studies have reported that insulin resistance may stimulate hepatic cholesterol secretion, biliary cholesterol supersaturated, and gallbladder movement disorder, thus promoting the formation of gallstones [30,36].

Furthermore, studies have shown that Leptin may be related to increased GSD prevalence caused by hypertension [37,38]. Leptin, an adipocyte-derived hormone, regulates blood lipids and glucose. Experimental research and population surveys indicated Leptin is closely related to hypertension [39] and cholelithiasis [38,40,41]. In patients with essential hypertension, serum leptin levels increase significantly with the severity of hypertension [37,42,43]. The increased concentration of Leptin can fortify hydrophilic bile salts, reduce hydrophobic bile salts and the circulating bile acid salt pool, making the cholesterol saturation of bile, which eventually leads to the formation of gallstones [44-46]. Furthermore, a high level of Leptin may cause leptin resistance, which will lead to the increased expression of sterol regulatory element-binding protein (SREBP) and a high level of LDL-C, thus accelerating the formation of gallstones [44,45]. The exact mechanism of the increased risk of GSD caused by hypertension needs to be further explored.

Our studies show that the relationship between hypertension and cholelithiasis is inconsistent among genders. Previous studies have found that the prevalence of GSD in women is higher than in men [47]. For this possible reason, female endogenous estrogen may participate in the liver cholesterol anabolism and promote crystallization nucleation, leading to gallstone formation [47]. In our study, subgroup analysis by gender found that hypertension is positively related to GSD in both men and women. Still, the effect size is relatively more prominent in women than in men, consistent with a cohort study conducted in South Korea [16]. On the contrary, a cross-sectional study found that hypertension was positively associated with GSD risk in females but not in males [48]. Further studies are needed to investigate the influence of gender on the association between hypertension and cholelithiasis.

Moreover, ATP-binding cassette transporters (including ABCA1, ABCG5, and ABCG8) function as efflux facilitators of phospholipids and hepatobiliary cholesterol, playing an essential role in developing GSD [49-51]. Claudia Huesca-Gómez et al. also showed an inverse correlation between *ABCA1/ABCG1* and essential arterial hypertension in patients with cIMT [52]. Besides, a single nucleotide polymorphism (SNP) rs11191548 near cytochrome P450 family 17 subfamilies A member 1 (*CYP17A1*) gene [53,54] is significantly associated with hypertension and hypercholesterolemia [55]. At the same time, variants in this gene are also related to biliary stones among overweight and diabetic subjects [56], suggesting a role of genetic factors in the association of hypertension with GSD.

Limitation

There are some limitations. Firstly, our study is a summary of cross-sectional research results, and thus the association between hypertension and GSD risk might be affected by potential confounders and reverse causality. Secondly, the heterogeneities among the studies were relatively high, which may partly affect the results. Thus, the results should be explained with caution.

Conclusion

The results of this mini-review support the association between hypertension and GSD. The higher the hypertension grade, the greater the risk of GSD. However, the role and mechanism of hypertension in cholelithiasis are not fully understood. More research is needed to explore the pathogenesis of this association.

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